

Web Material

Common Childhood Viruses and Pubertal Timing: The LEGACY Girls Study

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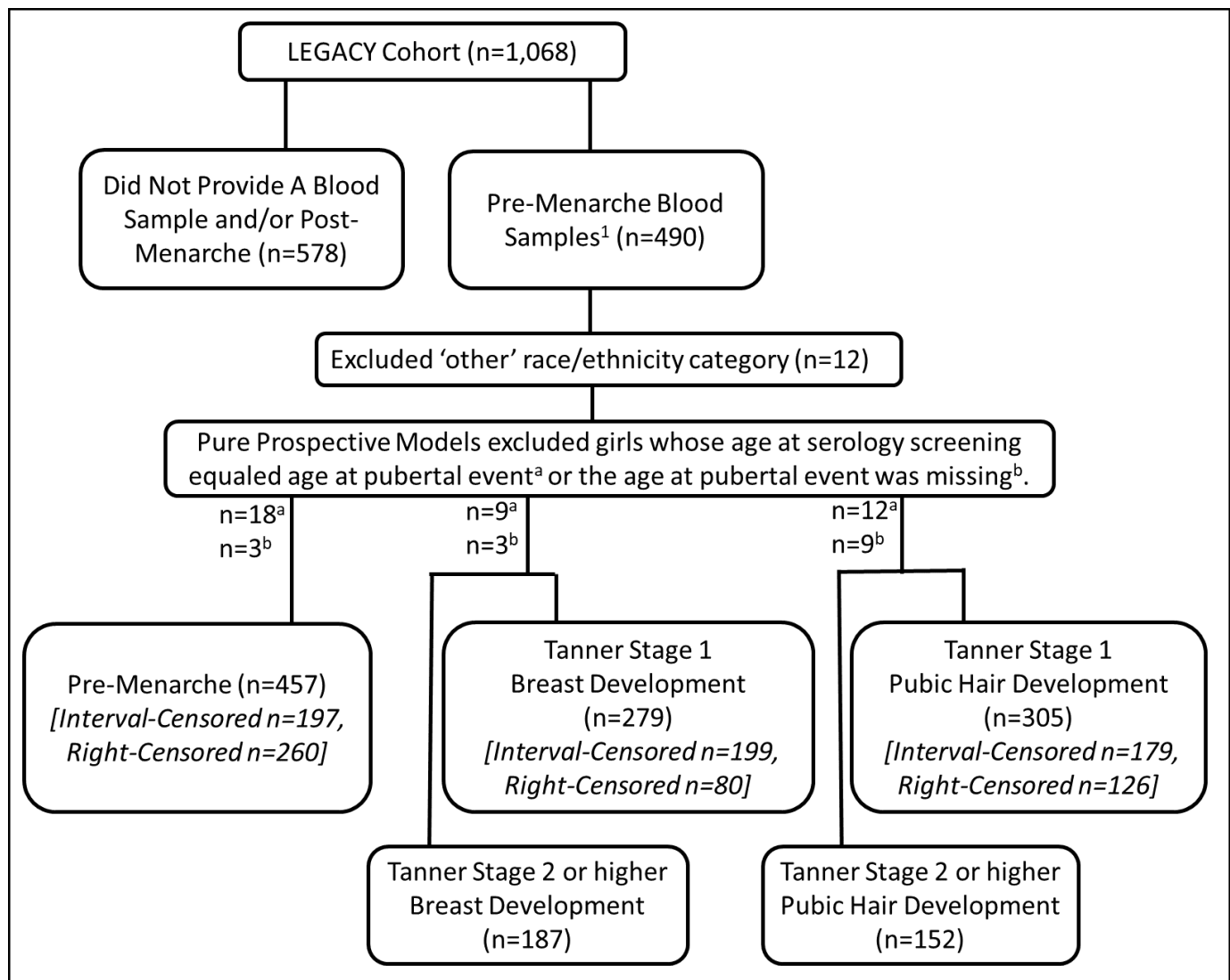
Web Table 1. Characteristics Between Those Who Provided Blood Samples Prior to Menarche Compared to Those Who Provided Blood Samples at/or After Menarche or No Blood Sample Available, LEGACY Girls Study (2011 – 2016)

Demographic Variables	First available blood samples <u>prior to Menarche</u> (N=490)		First available blood samples <u>at/or after Menarche or no</u> blood sample available (N=578)	
	No.	%	No.	%
Baseline Age^a	8.8 ± 2.0		10.2 ± 2.5	
Baseline BMI Percentile^a	45.8 ± 31.2		52.7 ± 29.9	
Missing	9	1.8	49	8.5
Baseline BMI Percentile				
<85th Percentile	412	84.1	425	73.5
≥85th Percentile	69	14.1	104	18.0
Missing	9	1.8	49	8.5
Race/Ethnicity				
Hispanic	72	14.7	124	21.5
Black non-Hispanic	31	6.3	48	8.3
White non-Hispanic	336	68.6	333	57.6
Asian non-Hispanic	39	8.0	54	9.3
Other	12	2.4	19	3.3
Maternal Education				
Some College/Vocational/ Technical/Less	126	25.7	170	29.4
Bachelor's Degree	173	35.3	212	36.7
Graduate Degree	185	37.8	176	30.4
Missing	6	1.2	20	3.5
Breast Cancer Family History^b				
None	240	49.0	285	49.3
Any	250	51.0	293	50.7

Body Mass Index, BMI

^aValues are expressed as mean (standard deviation).

^bWe classified daughter's breast cancer family history as the daughter having a first- or second-degree relative diagnosed with breast cancer.



Web Figure 1. The LEGACY Girl's Study Biomarker Study Flow Diagram. ¹The prospective biomarker study only screened those who had an available blood sample and had not reported menses at the time of the blood sample. Each outcome will independently add up to the total sample size of 490. For analyses, we excluded girls who identified as 'other' race/ethnicity from our analyses due to small sample size (n=12). In the "purely prospective" models, we excluded girls whose ^aage at serology screening equaled age at pubertal event or the ^bage at pubertal event was missing; therefore, 457 were included when modeling for menarche (none were left-censored), 279 were included when modeling for breast development (187 were left-censored), and 305 were included when modeling for pubic hair development (152 were left-censored). The "prospective+left-censored" model included girls from the "purely prospective" model *and* included retrospective puberty onset information from the mother for girls who were left-censored and girls whose age at serology equaled age at pubertal event.

Web Table 2. Association Between Viral Serology and Onset of Breast Development and the Onset of Pubic Hair Development in Girls by Varying BMI Adjustments, LEGACY Girls Study (2011 – 2016)

Viral Serology Measures	Model 2 ^a starting follow-up time at birth		Model 2a ^a without BMI adjustment		Model 2b ^a in participants <85 th BMI Percentile	
	HR	95% CI	HR	95% CI	HR	95% CI
<i>Onset of Breast Development</i>						
Categorical Viral Serology						
No Infection	1.00	Referent	1.00	Referent	1.00	Referent
CMV ⁺ only	2.12	(1.32, 3.40)	1.77	(1.07, 2.95)	1.98	(1.21, 3.22)
CMV ⁺ /EBV ⁺ coinfection only	1.04	(0.63, 1.72)	0.90	(0.51, 1.58)	0.99	(0.60, 1.62)
EBV ⁺ only	1.90	(1.15, 3.13)	1.62	(1.01, 2.62)	1.77	(1.01, 3.10)
HSV1 ⁺ and/or HSV2 ⁺	1.14	(0.61, 2.13)	1.00	(0.53, 1.91)	1.11	(0.58, 2.13)
All other infection combinations	1.64	(0.97, 2.75)	1.85	(1.01, 3.39)	1.08	(0.57, 2.06)
<i>Onset of Pubic Hair Development</i>						
Categorical Viral Serology						
No Infection	1.00	Referent	1.00	Referent	1.00	Referent
CMV ⁺ only	0.41	(0.24, 0.71)	0.43	(0.26, 0.72)	0.42	(0.23, 0.75)
CMV ⁺ /EBV ⁺ coinfection only	0.84	(0.48, 1.45)	0.89	(0.54, 1.46)	0.76	(0.41, 1.40)
EBV ⁺ only	0.76	(0.49, 1.18)	0.67	(0.44, 1.02)	0.87	(0.54, 1.39)
HSV1 ⁺ and/or HSV2 ⁺	0.42	(0.22, 0.81)	0.46	(0.24, 0.85)	0.42	(0.22, 0.81)
All other infection combinations	0.49	(0.24, 0.98)	0.55	(0.28, 1.07)	0.46	(0.20, 1.06)
<i>Onset of Menses</i>						
Categorical Viral Serology						
No Infection	1.00	Referent	1.00	Referent	1.00	Referent
CMV ⁺ only	1.49	(0.87, 2.57)	1.47	(0.90, 2.40)	1.61	(0.89, 2.90)
CMV ⁺ /EBV ⁺ coinfection only	1.45	(0.90, 2.33)	1.48	(0.90, 2.42)	1.57	(0.90, 2.74)
EBV ⁺ only	0.82	(0.51, 1.32)	0.95	(0.57, 1.59)	0.82	(0.47, 1.45)
HSV1 ⁺ and/or HSV2 ⁺	0.96	(0.53, 1.76)	1.19	(0.70, 2.01)	0.85	(0.46, 1.58)
All other infection combinations	0.65	(0.28, 1.52)	0.76	(0.25, 2.31)	0.56	(0.20, 1.56)

Body Mass Index, BMI; Confidence Interval, CI; Cytomegalovirus, CMV; Epstein Barr Virus, EBV; Hazard Ratio, HR; Herpes Simplex Virus 1, HSV1; Herpes Simplex Virus 2, HSV2

^aModel 2 is the “purely prospective” model from Table 3 which starts follow-up time at birth. Model 2a is without BMI adjustment and Model 2b is in participants <85th BMI percentile.

Web Table 3. Association Between Prospective Girls and Left Censored Girls by Sociodemographic Factors^a, LEGACY Girls Study (2011 – 2016)

Demographic Variables	First available blood samples prior to Menarche (Total n=490)		Breast Development				Pubic Hair				Menarche	
			Prospective ^c (n=279)		Left (n=187)		Prospective ^c (n=305)		Left (n=152)		Prospective ^c (n=457)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age at Blood Draw^d	9.8 ± 1.9		8.9 ± 1.6		11.2 ± 1.4		9.0 ± 1.6		11.2 ± 1.6		9.7 ± 1.9	
BMI Percentile at Blood Draw^{b,d}	46.1 ± 31.4		41.8 ± 30.0		50.8 ± 32.0		44.1 ± 30.9		48.6 ± 31.3		45.4 ± 31.1	
BMI Percentile at Blood Draw^b												
<85th Percentile	404	82.5	241	86.4	145	77.5	254	83.3	125	82.2	379	82.9
≥85th Percentile	75	15.3	30	10.8	39	20.9	44	14.4	24	15.8	68	14.9
Race/Ethnicity												
Hispanic	72	14.7	44	15.8	25	13.4	48	15.7	21	13.8	66	14.4
Black non-Hispanic	31	6.3	13	4.7	17	9.1	14	4.6	16	10.5	30	6.6
White non-Hispanic	336	68.6	198	71.0	130	69.5	215	70.5	104	68.4	322	70.5
Asian non-Hispanic	39	8.0	24	8.6	15	8.0	28	9.2	11	7.2	39	8.5
Other	12	2.4	0		0		0		0		0	
Maternal Education^b												
Some College/Vocational/Technical/Less	126	25.7	65	23.3	53	28.3	76	24.9	40	26.3	115	25.2
Bachelor's Degree	173	35.3	105	37.6	58	31.0	112	36.7	49	32.2	159	34.8
Graduate Degree	185	37.8	106	38.0	73	39.0	113	37.1	62	40.8	177	38.7
Categorical Viral Serology												
No Infection	206	42.0	109	39.1	89	47.6	125	41.0	71	46.7	195	42.7
CMV ⁺ only	66	13.5	39	14.0	23	12.3	37	12.1	23	15.1	60	13.1
CMV ⁺ /EBV ⁺ coinfection only	61	12.5	35	12.5	24	12.8	38	12.5	20	13.2	58	12.7
EBV ⁺ only	88	18.0	50	17.9	33	17.7	59	19.3	22	14.5	81	17.7
HSV1 ⁺ and/or HSV2 ⁺	29	5.9	21	7.5	7	3.7	22	7.2	5	3.3	27	5.9
All other infection combinations	40	8.2	25	9.0	11	5.9	24	7.9	11	7.2	36	7.9

Body Mass Index, BMI; Cytomegalovirus, CMV; Epstein Barr Virus, EBV; Hazard Ratio, HR; Herpes Simplex Virus 1, HSV1; Herpes Simplex Virus 2, HSV2

^aWe included in the table the distribution of sociodemographic factors that were significantly associated with our final regression models for breast development and for pubic hair development.

^bThere were 11 participants missing BMI data and 6 missing maternal education data.

^cThe percentage of girls who were right censored in our “purely prospective” analyses included 29% for breast development (n=80), 41% for pubic hair development (n=126), and 57% for age at menarche (n=260).

^dValues are expressed as mean (standard deviation)